

Highly Enantioselective Catalytic Acyl-Pictet-Spengler Reaction

Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *ASAP*.

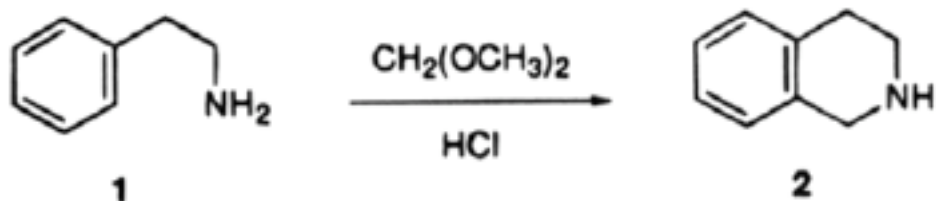
For Review of Pictet-Spengler Reaction :

Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

Yiqian Lian

8-12-04

Introduction to Pictet-Spengler Reaction

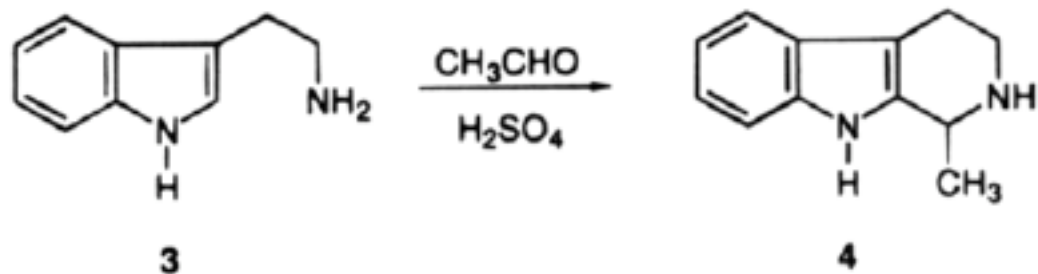


Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

- The reaction was originally utilized exclusively to prepare tetrahydroisoquinolines;
- Represented an established biosynthetic pathway;
- A standard method for the formation of tetrahydroisoquinolines.

For review: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

Introduction to Pictet-Spengler Reaction

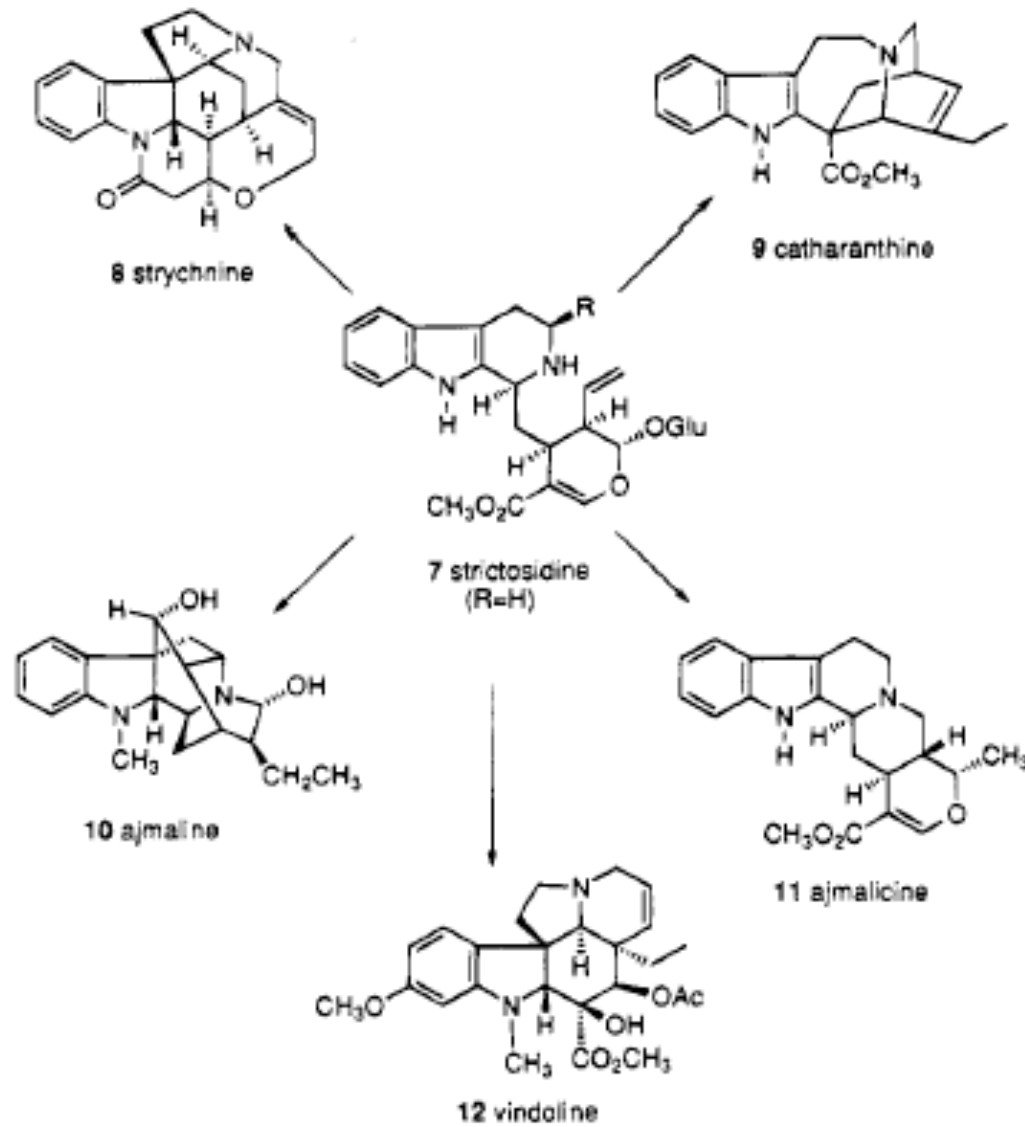


Tatsui, G. *J. Pharm. Soc. Jpn.* **1928**, 48, 92.

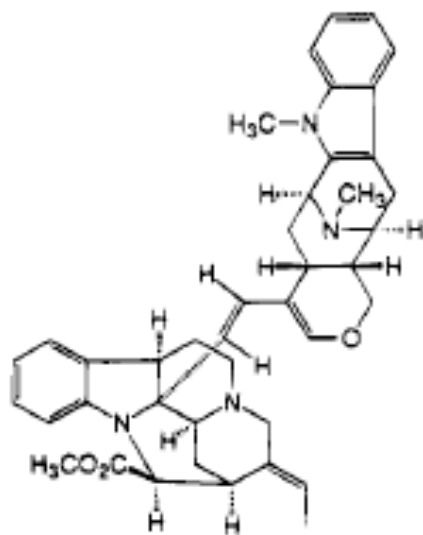
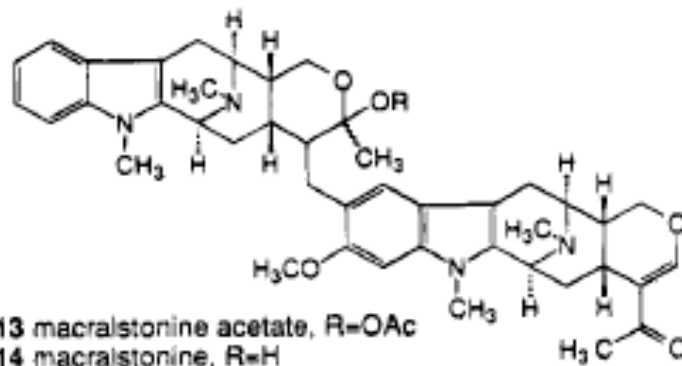
- Preparation of 1-methyl-1,2,3,4-tetrahydro- β -carboline with an indole base.
- An important method in the synthesis of indole alkaloid natural products.

For review: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, 95, 1797.

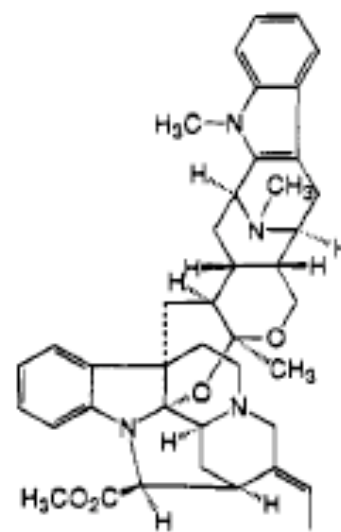
Some Indole Alkaloid Natural Products



More Examples of Indole Alkaloid Natural Products

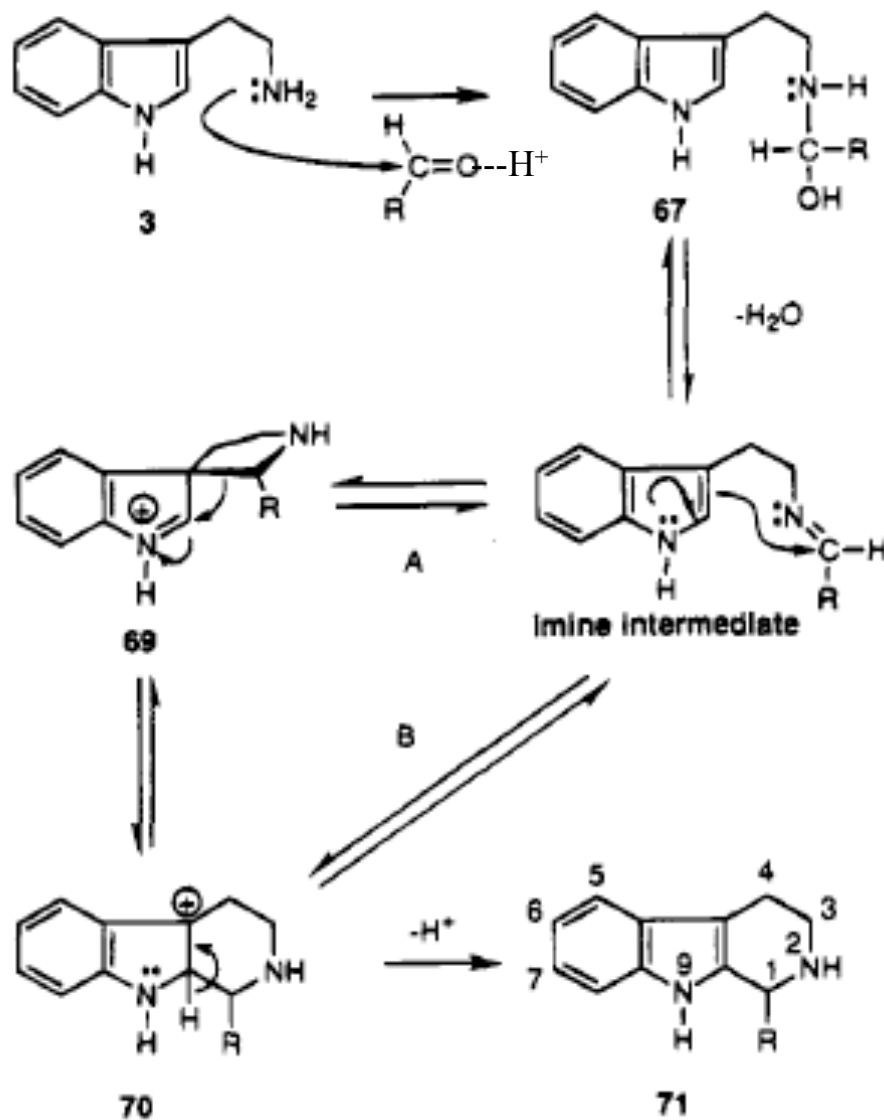


15 macrocarpamine

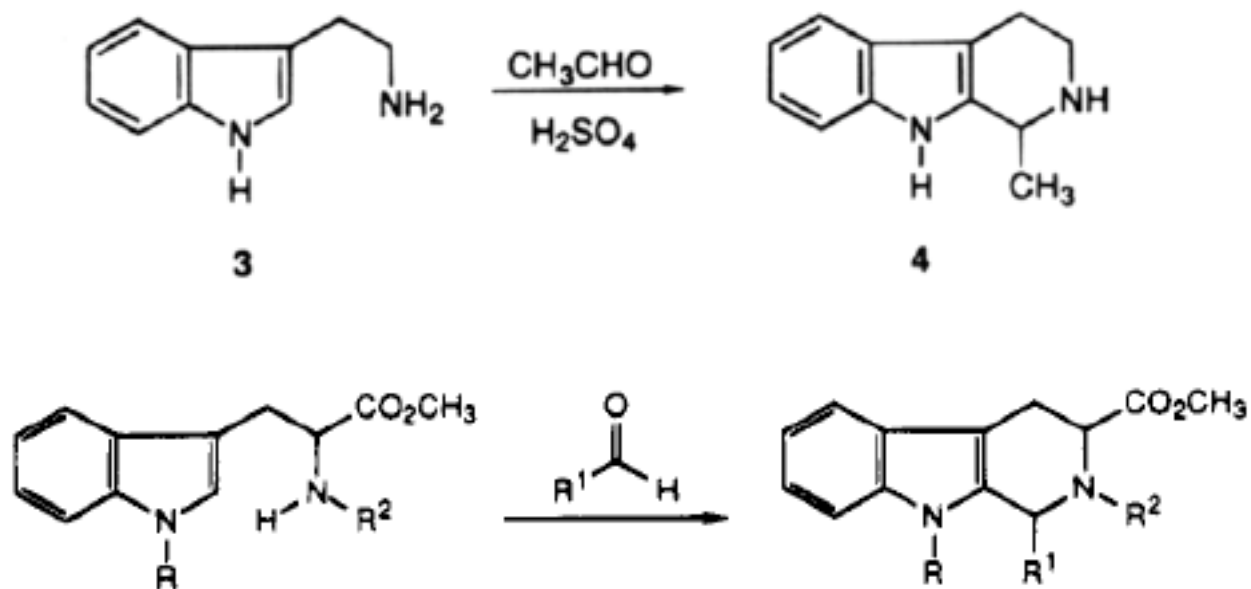


16 villalstonine

Mechanism of the Pictet-Spengler Condensation



Pictet-Spengler Reaction in Nonacidic Aprotic Media

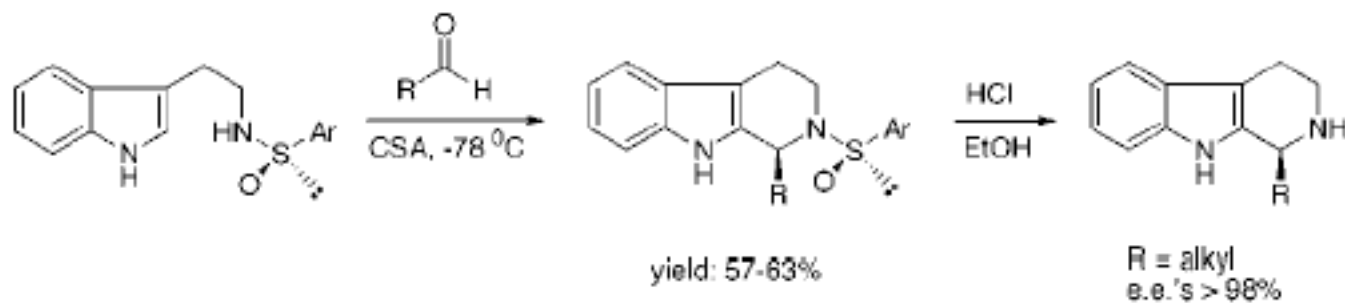
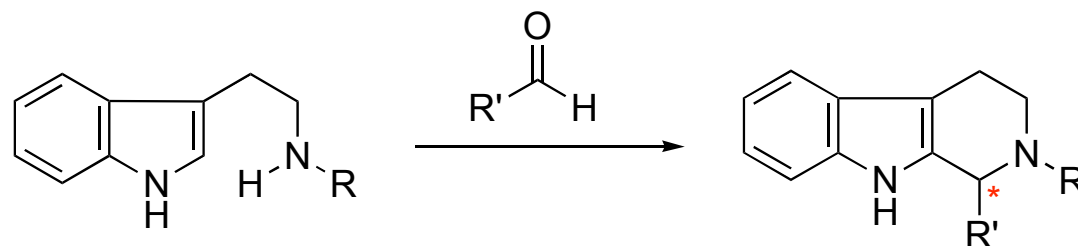


amine	R	R ²	aldehyde	product	R ¹	aprotic % yield	aqueous % yield
17	H	H	18	20	Ph	95	90
17	H	H	23	25	C ₆ H ₁₁	85	73
21	H	Bn	18	26	Ph	95	
21	H	Bn	23	27	C ₆ H ₁₁	87	
22	CH ₃	Bn	23	28	C ₆ H ₁₁	87	68
21	H	Bn	24	29	CH ₂ CH ₂ CO ₂ C ₂ H ₅	80	50

.. Heated in benzene at reflux, without the aid of acid catalysts.

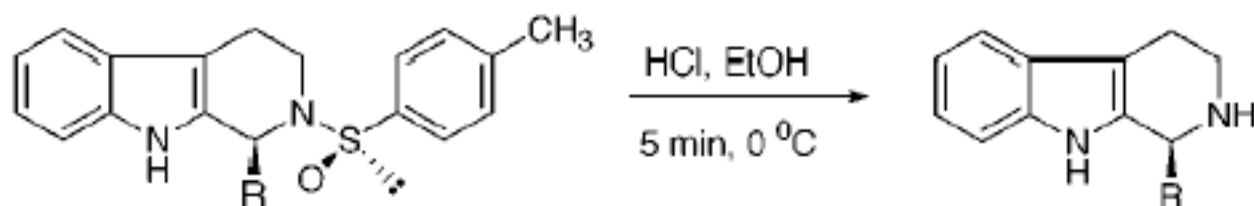
Cook, J. M. et al. JOC **1979**, 44, 535.

Diastereoselective Pictet-Spengler Reaction



Koomen. et al. OL **2000**, 2,
1955.

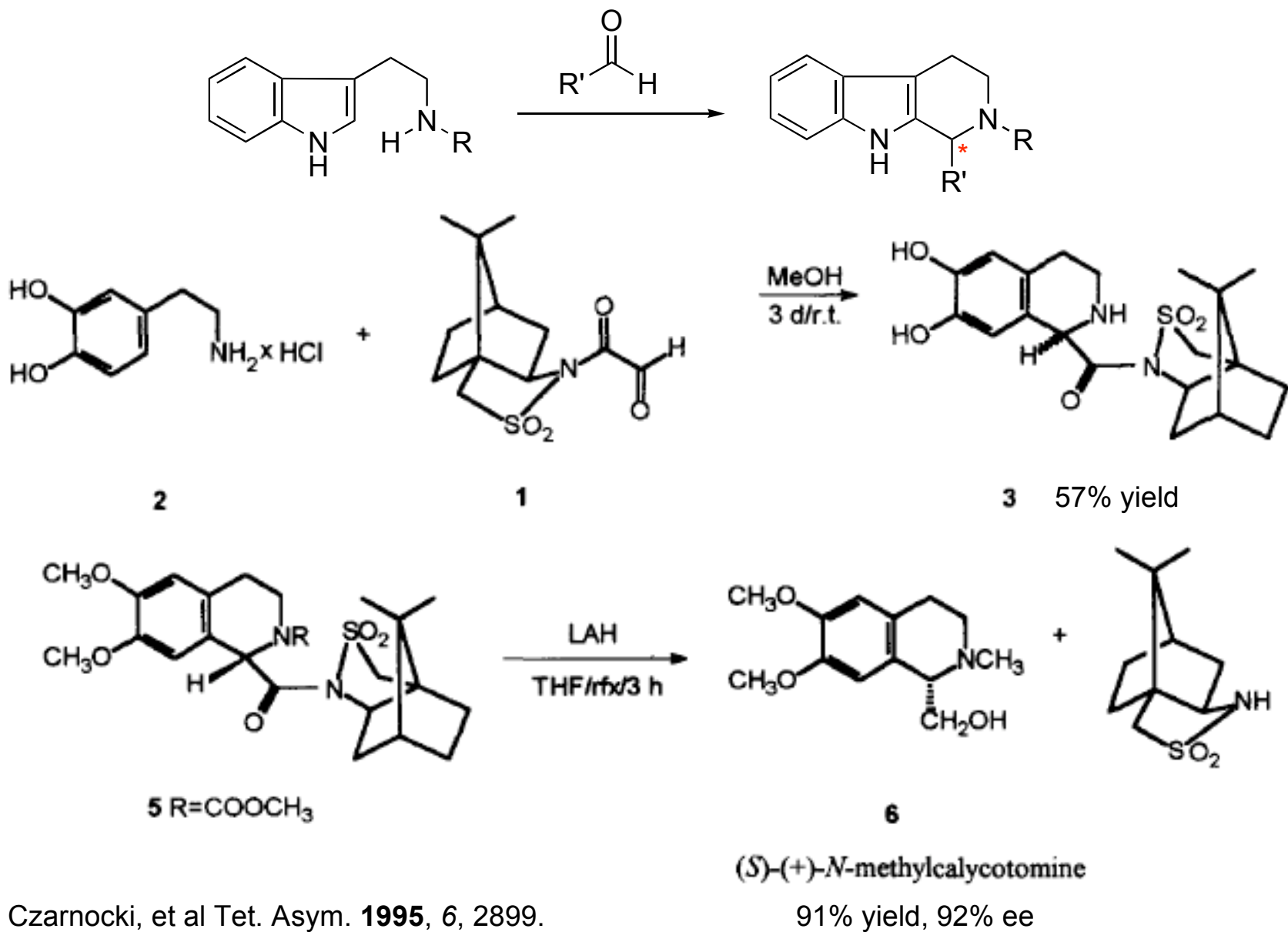
Chiral N-protective Group



no.	R	yield (%) ^a	ee ^b	[α] _D
(-)- 18	methyl	89	>98%	-44.0 ^c
(-)- 19	ethyl	93	>98%	-62.6
(-)- 20	propyl	91	>98%	-30.0
(-)- 21	butyl	93	>98%	-65.8
(-)- 22	pentyl	82	>98%	-40.0
(-)- 23	isobutyl ²³	90	>98%	-47.1
(-)- 24	isopropyl	93	>98%	-58.3
(-)- 25	cyclohexyl	86	>98%	-68.5

^a After chromatography. ^b As determined with ¹H NMR using (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol. ^c Lit. (*S*)-**18**: [α]_D = -41.²⁴

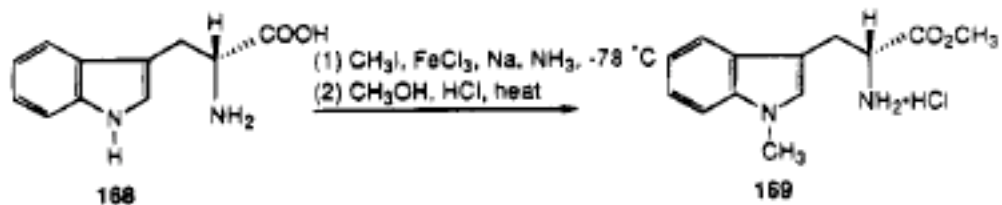
Chiral Aldehyde



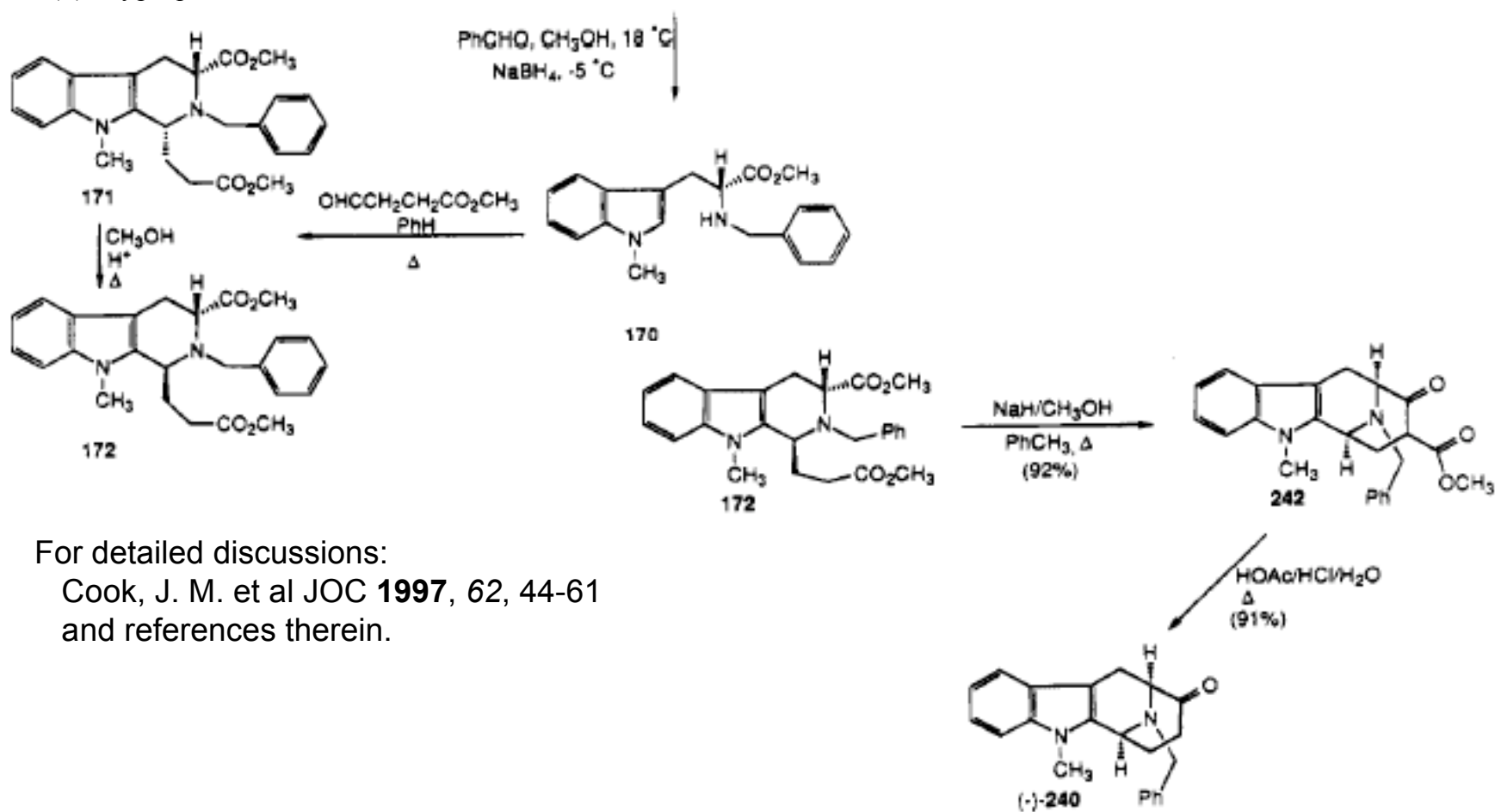
Czarnocki, et al Tet. Asym. **1995**, 6, 2899.

91% yield, 92% ee

Diastereoselective Pictet-Spengler Reaction of Tryptophan Esters



D-(+)-Tryptophan



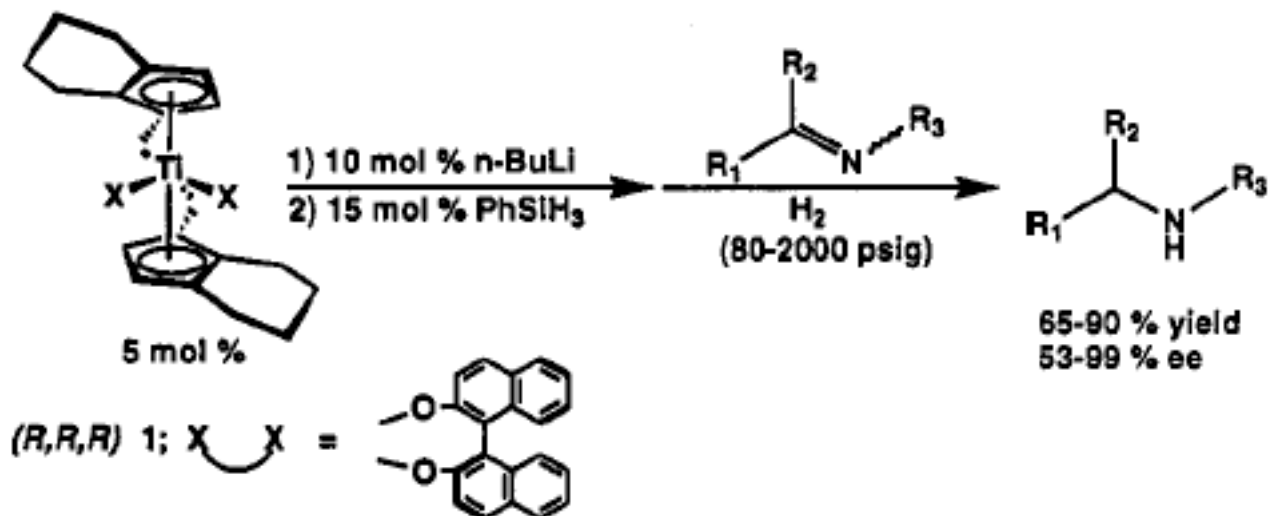
For detailed discussions:

Cook, J. M. et al JOC **1997**, 62, 44-61

and references therein.

Enantioselective, Catalytic Approaches

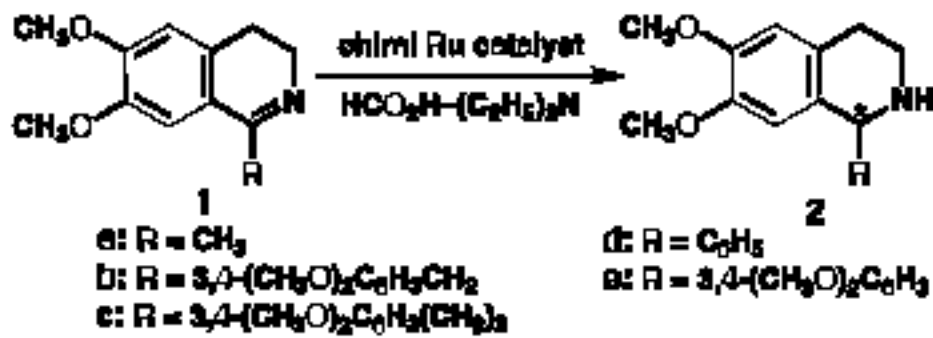
- ◆ Mostly restricted to asymmetric hydrogenation of cyclic imines



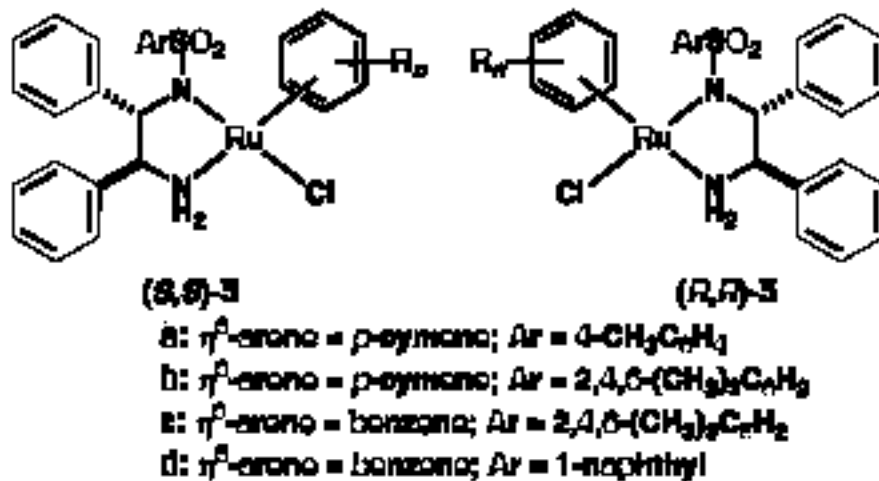
Entry	Imine	Amine	Pressure (psig)	T (° C)	Yield (%)	ee (%)	(±)
4			2000	65	82	98	(-)
			80	65	79	95	(-)
5			500	23	83	99	(+)
			80	65	72	99	(+)
6			80	50	79	99	(+)

Buckwald, et al. JACS **1994**, *116*, 8952.

Enantioselective, Catalytic Approaches



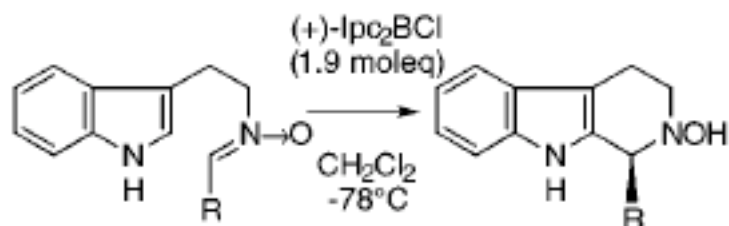
72-99% yield
77-97% ee



Noyori, et al. JACS 1996, 118, 4916.

Pictet-Spengler Reaction of Nitrones Catalyzed by (+)-Ipc₂BCl

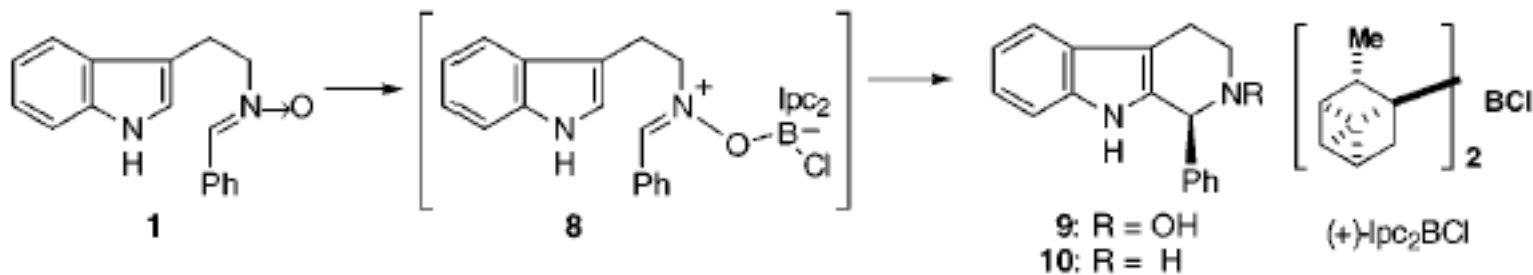
One example of a chiral Lewis acid-mediated Pictet-Spengler reaction;



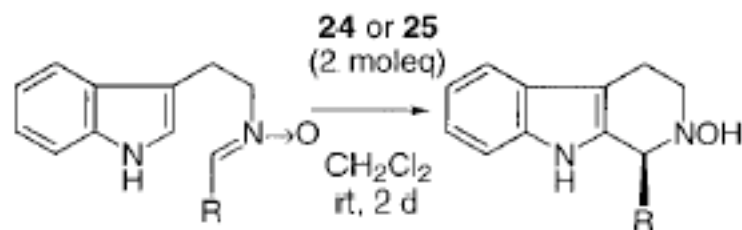
- | | |
|---|--|
| 1: R = Ph | 9: R = Ph |
| 2: R = <i>p</i> -MeO-C ₆ H ₄ | 15: R = <i>p</i> -MeO-C ₆ H ₄ |
| 3: R = <i>p</i> -NO ₂ -C ₆ H ₄ | 16: R = <i>p</i> -NO ₂ -C ₆ H ₄ |
| 4: R = 1-Naphthyl | 17: R = 1-Naphthyl |
| 5: R = Me | 18: R = Me |
| 6: R = <i>i</i> Bu | 19: R = <i>i</i> Bu |

Nakagawa, et al. JOC **1998**, 6348.

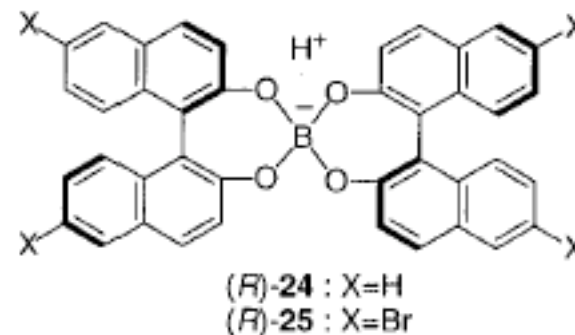
entry	nitronone	time (h)	<i>β</i> -carboline	
			yield (%)	% ee
1	1	6	9 (92)	75 (<i>S</i>)
2	2	3	15 (65)	90 (<i>S</i>)
3	3	1	16 (81)	0.6
4	4	1	17 (94)	86 (<i>S</i>)
5	5	3	18 (91)	43 (<i>S</i>)
6	6	4	19 (75)	35 (<i>S</i>)



Nitrones Catalyzed by Bronsted Acid-Assisted Lewis Acids



- | | |
|--|---|
| 1: R = Ph | 9: R = Ph |
| 2: R = <i>p</i> -MeO-C ₆ H ₄ | 15: R = <i>p</i> -MeO-C ₆ H ₄ |
| 3: R = <i>p</i> -NO ₂ -C ₆ H ₄ | 16: R = <i>p</i> -NO ₂ -C ₆ H ₄ |
| 4: R = 1-Naphthyl | 17: R = 1-Naphthyl |
| 5: R = Me | 18: R = Me |
| 6: R = <i>i</i> -Bu | 19: R = <i>i</i> -Bu |

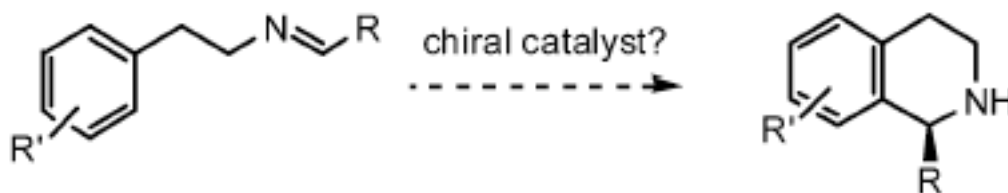


entry	nitronone	Lewis acid	results		recovery of nitronone (%)
			yield (%)	% ee ^a	
1	1	(<i>R</i>)- 24	9 (81)	73 (<i>S</i>)	18
2	2	(<i>R</i>)- 24	15 (39)	91 (<i>S</i>)	44
3	3	(<i>R</i>)- 24	16 (75)	74 (<i>S</i>)	8
4	4	(<i>R</i>)- 24	17 (59)	31 (<i>S</i>)	26
5	5	(<i>R</i>)- 24	18 (94)	15 (<i>R</i>)	
6	6	(<i>R</i>)- 24	19 (68)	50 (<i>S</i>)	14
7	1	(<i>S</i>)- 24	9 (82)	78 (<i>R</i>)	7
8	1	(<i>R</i>)- 25	9 (84)	77 (<i>S</i>)	

Nakagawa, et al. JOC **1998**, 6348.

- “ The only reported example of a chiral Lewis acid-mediated (reagent-controlled enantioselective) Pictet-Spengler reaction;
- “ Used superstoichiometric quantities of an enatioenriched boron reagent;
- “ Limited to N_β-hydroxytryptamine-derived nitrones.

The Challenge for an Asymmetric Catalytic Variant

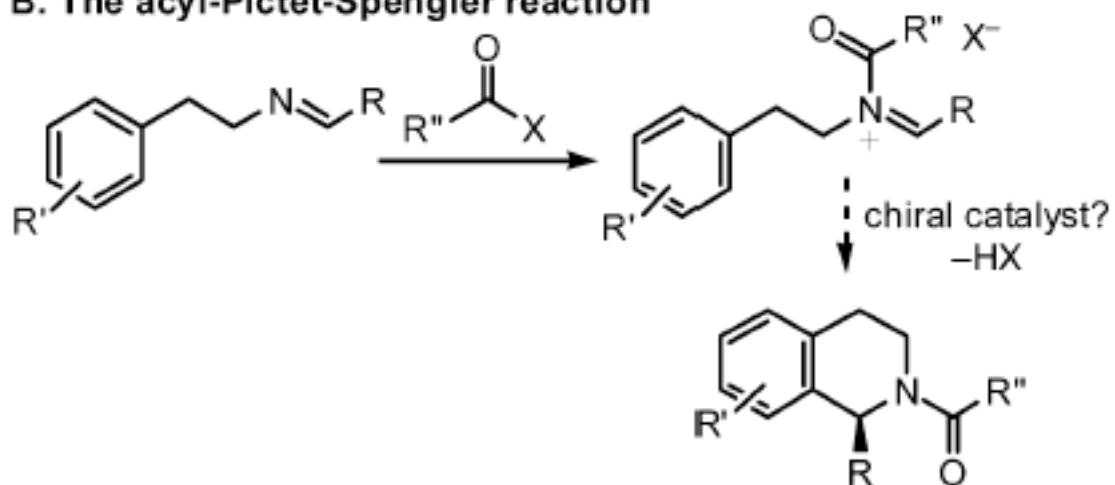


- The challenge appears to be associated with the low reactivity of the imine substrate;
- Most often, strong Brønsted acids are employed to promote the racemic pathway; the few reported examples of Lewis acid catalysis involve highly reactive agents, unmodified by donor ligands. In addition, high reaction temperatures are often required.
- A screen of potential chiral catalysts for this transformation did not afford any useful leads;
(Catalysts: chiral ureas and thioureas, (salen)aluminum complexes and other chiral ligand-metal complexes; Substrates: derived from condensation of aromatic and aliphatic aldehydes with tryptamines and electron-rich arylethyl amines.)
- More reactive variants are needed to proceed under relatively mild conditions;

The Possible Solution ...

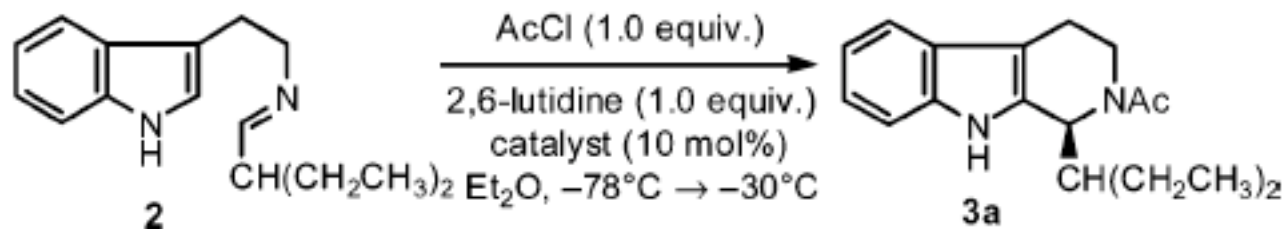
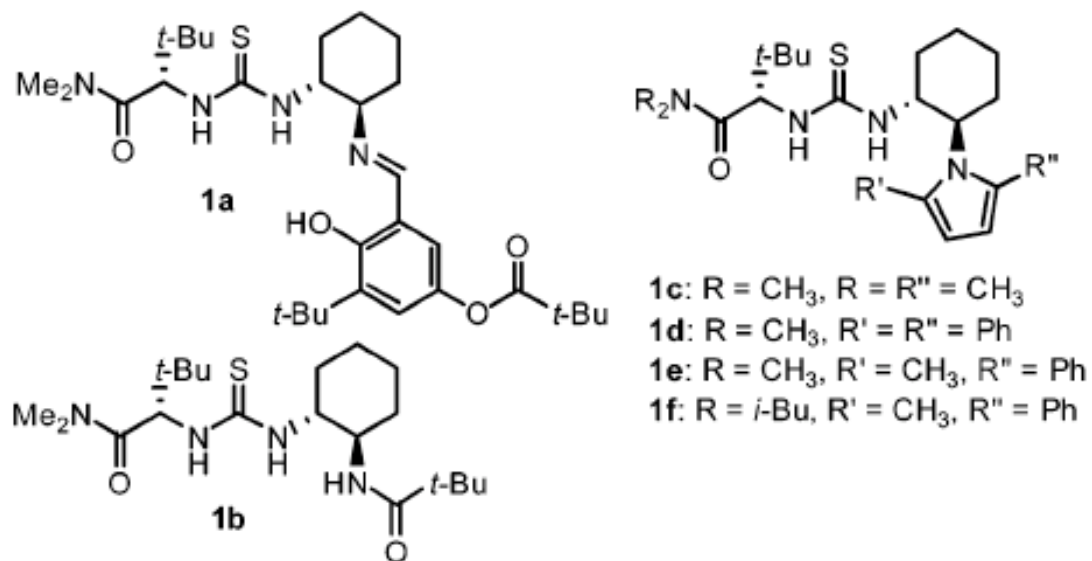
“ A general strategy for enhancing the reactivity in processes involving imine or iminium intermediates involves generation of the corresponding *N*-acyliminium ions.

B. The acyl-Pictet-Spengler reaction



Chiral thiourea catalyst?

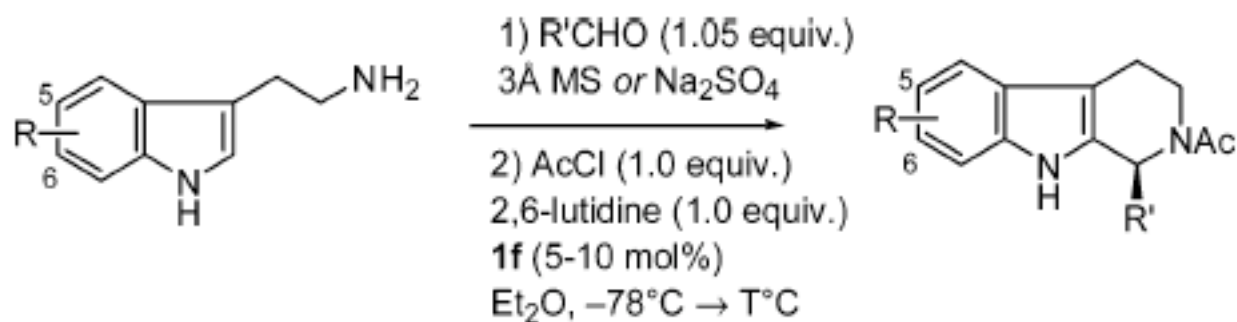
Optimization of Thiourea Catalyst Structure



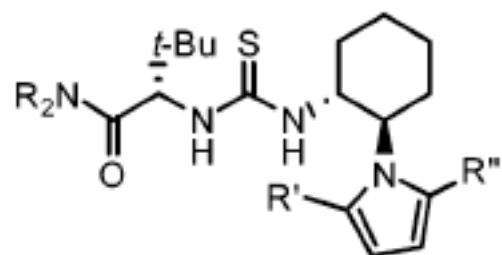
catalyst	yield (%) ^a	ee (%) ^b
1a	65	59
1b	45	61
1c	65	77
1d	55	71
1e	70	93
1f	70	93

Highly Enantioselective Catalytic Acyl-Pictet-Spengler Reaction

Table 2. Asymmetric Acyl-Pictet–Spengler Reactions Catalyzed by **1f**



product	R	R'	T (°C)	yield (%) ^a	ee (%) ^b
3a	H	CH(CH ₂ CH ₃) ₂	-30	65 ^c	93
3b	H	CH(CH ₃) ₂	-40	67 ^d	85
3c	H	<i>n</i> -C ₅ H ₁₁	-60	65 ^d	95
3d	H	CH ₂ CH(CH ₃) ₂	-60	75 ^d	93
3e	H	CH ₂ CH ₂ OTBDPS	-60	77 ^d	90
3f	5-MeO	CH(CH ₂ CH ₃) ₂	-40	81 ^c	93
3g	6-MeO	CH(CH ₂ CH ₃) ₂	-50	76 ^d	86



1f: R = *i*-Bu, R' = CH₃, R'' = Ph

Still Much Work to Be Done...

- “ Highly enantioselective catalytic acyl-Pictet-Spengler reaction was achieved.
- “ The ability to activate a weakly Lewis basic N-acyliminium ion toward enantioselective Pictet-Spengler reaction using a chiral hydrogen donor presents new opportunities for catalysis.
- “ The mechanism of the transformation?
- “ The scope of the reaction?
- “ Application of the enantioselective reaction in indole alkaloid synthesis...